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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,704	02/07/2000	Paul S. Uster	5325-0162.30	9201

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/498,704	Uster
Examiner	**Art Unit**
Gollamudi S. Kishore, Ph.D	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 17, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The request for reconsideration dated 1-17-02 is acknowledged.

Claims included in the prosecution are 1-30.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

2. Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marin (5,213,804) in combination with Mori (Cancer Chemther Pharmacol, 1995) of record, or vice versa.

Martin discloses a liposome compositions containing a phospholipid, 1-20 mol. % of a amphipathic lipid derivatized with PEG. The composition is for localizing an imaging or anti-tumor agent for therapeutic and diagnostic purposes (note the abstract, col. 1, line 34 et seq., Examples and claims).

What is lacking in Martin is the use of a radiosensitizer as the active agent

Mori while disclosing liposomes containing dipalmitoyl-5-fluoro-2-deoxyuridine teaches that treatment of lung metastasis bearing mice with the this composition resulted in

significant increase in the median survival time of treated mice as compared to control mice (note the abstract and Materials and Methods).

What is lacking in Mori is the inclusion of lipid derivatized PEG.

The use of the radio sensitizer as the anti-tumor agent in the compositions of Martin would have been obvious to one of ordinary skill in the art because of its effectiveness shown by Mori. Alternately to use the lipid derivatized polymer in the liposomal compositions of Mori would have been obvious to one of ordinary skill in the art because of the increase in the blood circulation time of the liposomes as shown by Martin (note col. 14). Although Mori does not teach other halogen derivatives of deoxyuridine, in the absence of showing otherwise, it is deemed obvious to one of ordinary skill in the art to use halogens other than fluorine taught by Mori with a reasonable expectation of obtaining at least similar results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Martin is specifically concerned with providing liposomes that evade uptake by the reticuloendothelial system (RES) to achieve a long blood circulation lifetime for extravasation into the tumor and that incorporation of a lipid-derivatized radiosensitizer into the lipid bilayer of the liposomes results in radiosensitizer molecules extending from the external surface of the liposomes; therefore, according to applicant, the presence of radiosensitizer molecules on the outer surface compromises the evasion properties of the liposomes, since the agent may not be completely

masked from recognition and the liposomes are susceptible to recognition and removal by the RES. Further according to applicant, modification of Martin to include the lipid prodrug of Mori would compromise the desired extended blood circulation lifetime of the liposomes, defeating the purpose of the liposome composition of Martin.

These arguments are not found to be persuasive for the following reasons. First of all, these arguments are not followed by any evidence, and therefore, deemed to be just speculative. Secondly, Martin on col. 2, line 54 et seq., clearly indicate that several factors such as liposome size, charge, degree of unsaturation of the lipids, surface moieties; the purpose of the attachment of PEG according to Martin is to see that these factors do not come into play because these are masked by PEG such that the RES system does not recognize these factors. This purpose is very clear when Martin states that the vesicles of his invention contain 1-20 mole percent of a vesicle forming lipid derivatized by a hydrophilic polymer (the same percentage of PEG as applicant) and that the compound is either associated with the liposome membrane or encapsulated within the internal aqueous compartment of the liposome as noted from col. 3, lines 42-50. Furthermore, PEG is a polymer and a macromolecule compared to the radiosensitizer such as the deoxyuridine compound and it is logical that PEG containing repeating units of ethylene glycol units will extend further on the liposomal surface than the deoxyuridine compound. In addition, the examiner points out that in Mori, the lipid derivatized deoxyuridine derivative was shown to perform it's function in liposomes in spite of the liposomes they are in, are attached to

monoclonal antibodies on the external surface of the liposomes. Antibodies which are proteins are macromolecules just as the hydrophilic polymer, PEG. The examiner therefore, disagrees applicant's characterization that the purpose of liposome composition in Martin is compromised by the inclusion of a radiosensitizer.

Applicant argues that Mori teaches that dpFUdR when incorporated into liposomes has a decreased therapeutic index due to increased toxicity. This argument is not found to be persuasive since Mori in subsequent lines (page 455, col. 1, line 3 et seq.) clearly state the reason for the increased toxicity. According to Mori, this is because of the predominant localization of the prodrug in the *liver* macrophages and the subsequent release from those cells of the parent drug FudR into the blood. This statement in fact strengthens the examiner's position that one of ordinary skill in the art would be motivated to include PEG on the surface of the liposomes containing the deoxyuridine derivative since the liposome escape liver (RES) and reach the site where it is needed without exhibiting the toxicity since liver is avoided. Applicant further argues that Mori is concerned with providing a liposome composition that targets an organ, such as the lung, by virtue of an antibody attached to the liposome surface and that the antibody must be accessible or unhindered in order to achieve a targeting effect and therefore, modification of the liposomes as described by Mori to include a polymer-derivatized lipid does not make sense. The examiner disagrees. First of all, as pointed out above, one of ordinary skill in the art would be motivated to decrease the dpFUdR toxicity which according to Mori, is because of the liver macrophages taking

up this compound, by PEG taught by Martin so that the liposomes avoid liver. Secondly, applicant's statement is not followed by any experimental data and therefore, is deemed to be a speculation since attachment of both antibodies and PEG to liposomal surface is known in the art; the examiner cites the references of Allen (5,527,528) and Tagawa (5,264,221) in this context (see the figures and col. 9, line 56 et. Seq. Of Allen and Examples of Tagawa). Furthermore, it is within the skill of the art not to attach a targeting ligand to the liposome surface if the specific targeting is not desired.

3. Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marin (5,213,804) in combination with Mori (Cancer Chemther Pharmacol, 1995) of record, or vice versa as set forth above, further in view of Kassis (5,077,034) of record.

As pointed out above, Mori does not teach iodine derivatives of deoxyuridine as the radiosensitizer. One of ordinary skill in the art would be motivated to use halogens other than fluorine taught by Mori with a reasonable expectation of obtaining at least similar results since Kassis teaches that the halogen derivatives of deoxyuridine, iodo-deoxyuridine derivative in particular is effective in the treatment and diagnosis of tumors (note the abstract, Examples and claims).

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants' arguments with regard to Martin and Mori have been addressed

above. Applicants argue that Kassis is silent with respect to liposomes. The examiner agrees and points out that Martin and Mori both teach the use of the liposomes.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

March 28, 2002